

ACUTE TOXICITY SUMMARY

TOLUENE

(methyl benzene, methyl benzol, phenyl methane, toluol)

CAS Registry Number: 108-88-3

I. Acute Toxicity Summary (for a 1-hour exposure)

<i>Inhalation reference exposure level</i>	37,000 µg/m³
<i>Critical effect(s)</i>	headache, dizziness, slight eye and nose irritation
<i>Hazard Index target(s)</i>	Nervous System; Eyes; Respiratory System; Reproductive/developmental

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

<i>Description</i>	colorless liquid
<i>Molecular formula</i>	C ₇ H ₈
<i>Molecular weight</i>	92.13
<i>Density</i>	0.861 g/cm ³ @ 25°C (Low <i>et al</i> , 1988)
<i>Boiling point</i>	111°C
<i>Melting point</i>	-95°C
<i>Vapor pressure</i>	28.1 mm Hg @ 25°C (USEPA, 1984)
<i>Flashpoint</i>	4° C, closed cup
<i>Explosive limits</i>	upper = 7% lower = 1.27%
<i>Solubility</i>	miscible in organic solvents
<i>Odor threshold</i>	1.6 ppm (geometric mean) (AIHA, 1989)
<i>Odor description</i>	sour, burnt (AIHA, 1989)
<i>Metabolites</i>	hippuric acid
<i>Conversion factor</i>	1 ppm = 3.75 mg/m ³ @ 25°C

III. Major Uses or Sources

Toluene occurs naturally as a component of crude oil and is produced in petroleum refining and coke oven operations. It is used in household aerosols, nail polish, paints and paint thinners, lacquers, rust inhibitors, adhesives, and solvent based cleaning agents. Toluene is also used in printing operations, leather tanning, and chemical processes. Benzene and other polycyclic aromatic hydrocarbons (PAHs) are common contaminants of toluene. Toluene is considered a sentinel chemical for benzene exposure.

IV. Acute Toxicity to Humans

Dysfunction of the central nervous system and narcosis are the major effects of acute exposure to toluene (ATSDR, 1989). Irritation of the skin, eye, and respiratory tract can also result. Inhalational abuse of toluene with high level exposure for long periods of time has produced progressive and irreversible changes in brain structure and function (Spencer and Schaumberg, 1985).

Two separate workplace incidents involving acute inhalation exposure to toluene in several workers resulted in effects of euphoria, drunkenness, dizziness, nausea, confusion, incoordination, drowsiness, and loss of consciousness (Longley *et al.*, 1967). The toluene concentrations were estimated at 10,000 to 30,000 ppm (40,000 to 110,000 mg/m³) although no actual measurements were made. No long-term follow-up of the exposed workers was conducted.

Reaction time and perceptual speed were studied in 12 young male subjects exposed by inhalation to toluene concentrations ranging from 100 to 700 ppm (400 to 3,000 mg/m³), each for a 20-minute interval (Gamberale and Hultengren, 1972). Statistically significant impaired reaction time was apparent following exposure to 300 ppm (1,000 mg/m³) toluene. A statistically significant impairment in perceptual speed was observed at 700 ppm toluene. No effects were observed at 100 ppm.

Two groups of middle aged workers, one with previous occupational exposure to solvents and one without, were exposed once to 100 ppm (400 mg/m³) of toluene for 6.5 hours (Baelum *et al.*, 1985). Fatigue, sleepiness, a feeling of intoxication, and eye, nose and throat irritation were reported. Decrements in manual dexterity, color discrimination, and accuracy in visual perception were also observed. Greater sensitivity to toluene was noted for those subjects with previous solvent exposure.

Nasal mucus flow, lung function, psychometric performance, and subjective responses were studied in 16 young healthy males exposed to toluene concentrations ranging from 10 to 100 ppm (40 mg/m³ to 400 mg/m³) for 6 hours (Andersen *et al.*, 1983). Headaches, dizziness, a feeling of intoxication, and slight eye and upper respiratory irritation were reported at 100 ppm. The subjects also reported that it became more difficult to participate in the battery of psychometric tests and that their reaction time felt impaired at 100 ppm. No significant objective changes compared to control exposures were observed in the performance test results. No symptoms were reported at 10 and 40 ppm.

A battery of neurobehavioral and performance tests was conducted among 42 young men and women exposed by inhalation for 7 hours to 0, 75, and 150 ppm (0, 280, and 560 mg/m³) toluene (Echeverria *et al.*, 1989). Statistically significant decrements in visual short term memory, visual perception, and psychomotor skills were observed at 150 ppm compared to control exposures. A dose-dependent increase in subjective symptoms of headache and eye irritation was also observed.

Wilson (1943) reported that workers exposed to concentrations of commercial toluene ranging from 50 to 200 ppm (200 to 750 mg/m³) for periods of 1 to 3 weeks experienced headaches, lassitude, and loss of appetite. At 200 to 500 ppm (750 to 2,000 mg/m³), symptoms of nausea,

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bad taste in the mouth, slightly impaired coordination and reaction time, and temporary memory loss were also observed. Exposure to 500 to 1,500 ppm (2,000 to 5,600 mg/m³) resulted in palpitations, extreme weakness, pronounced loss of coordination, and impaired reaction time. Red blood cell counts were decreased and there were 2 cases of aplastic anemia. The hematologic effects were most likely caused by benzene impurities (ACGIH, 1986).

Three volunteer subjects exposed by inhalation to toluene concentrations ranging from 50 to 100 ppm (200 to 400 mg/m³), 8 hours per day, 2 times per week over 8 weeks experienced fatigue, drowsiness, and headaches (von Oettingen *et al.*, 1942). At 200 to 800 ppm (750 to 3,000 mg/m³), symptoms of muscular weakness, confusion, impaired coordination, paresthesia, and nausea were also reported. After exposure to 800 ppm, all 3 subjects reported considerable after-effects (severe nervousness, muscular fatigue, and insomnia) lasting several days.

Predisposing Conditions for Toluene Toxicity

Medical: Since toluene is metabolized by the liver, persons with liver disease may be sensitive to its acute effects (ATSDR, 1993). Persons with preexisting neurologic or heart disease may also be at increased risk for adverse effects resulting from exposure to toluene (Reprotext, 1999).

Chemical: Because salicylates and alcohol competitively inhibit toluene metabolism, concurrent use of these substances may increase susceptibility to toluene toxicity (ATSDR, 1993). Persons using over-the-counter bronchial dilators containing epinephrine might be more sensitive to arrhythmogenic effects (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

The 1-hour LC₅₀ for toluene in the rat is 26,700 ppm (100,000 mg/m³) (Pryor *et al.*, 1978). The 6-hour LC₅₀s in rats and mice are 4,618 ppm (17,320 mg/m³) and 6,949 ppm (26,060 mg/m³), respectively (Bonnet *et al.*, 1982). The 8-hour LC₅₀ is 5,300 ppm (19,900 mg/m³) in the mouse (Svirbely *et al.*, 1943).

Attention deficits and impairment of visual-motor abilities were observed in 6 macaque monkeys exposed by inhalation for 50 minutes to 2,000-4,500 ppm (7,500-17,000 mg/m³) toluene (Taylor and Evans, 1985). Expired carbon dioxide increased in a dose-dependent manner from 100 to 3,000 ppm (400 to 11,000 mg/m³). The investigators stated that changes in expired carbon dioxide may provide evidence of combined behavioral, respiratory, sensory, and metabolic effects.

Dose-dependent decreases in behavioral performance and central nervous system depression were observed in mice and rats exposed by inhalation to toluene at concentrations ranging from 2,600 to 12,000 ppm (9,800 to 45,000 mg/m³) for up to 3 hours (Bruckner and Peterson, 1981). Younger animals were more susceptible to toluene toxicity and mice were more sensitive than rats of the same age.

Kishi *et al.* (1988) used the shock avoidance response test to study behavioral effects in rats. Inhalation exposure to 125 ppm (469 mg/m³) toluene for 20 minutes resulted in a considerable decrease in the effective avoidance response rate.

Hearing loss was observed in rats after exposure to 1,000 ppm (4,000 mg/m³) toluene, 14 hours per day for 2 weeks (Pryor *et al.*, 1984).

VI. Reproductive or Developmental Effects

Toluene is listed under the California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a developmental toxicant. Most of the information concerning the adverse developmental effects of toluene in humans comes from case reports among children of deliberate toluene “sniffers.” Children whose mothers had inhaled large quantities of toluene during pregnancy were found to have microencephaly, facial and limb abnormalities, attention deficits, hyperactivity, developmental delay with greater language impairment, and growth retardation (Hersch *et al.*, 1985; Hersch, 1989). Multiple solvent and/or other substance abuse may have contributed to the observed abnormalities. Growth retardation, craniofacial abnormalities, and hyperchloremic acidosis were observed in the children of women with severe renal tubular acidosis induced by chronic paint sniffing (Goodwin, 1988). Preterm delivery, perinatal death, and growth retardation were significantly increased among 21 newborns exposed to toluene as a result of maternal inhalation abuse (Wilkins-Haug and Gabow, 1991). A case-referent study of women occupationally exposed to organic solvents, including toluene, reported increased incidences of urogenital, gastrointestinal, and cardiac anomalies in their children (McDonald *et al.*, 1987). Although toluene was considered to be the most likely teratogenic agent, concurrent exposures to other developmental toxicants make this conclusion difficult to support.

There are several animal studies of varying quality on the reproductive and developmental toxicity of toluene. A complete review of the developmental toxicology of toluene is available (Donald *et al.*, 1991). Selected studies are summarized below.

Shigeta *et al.* (1982) reported statistically significant increases in the number of fetal resorptions observed in the offspring of mice exposed by inhalation to 100 ppm (400 mg/m³) toluene for 6 hours per day on days 1-17 of gestation. Exposure at 1,000 ppm (4,000 mg/m³) resulted in a statistically significant increase in the incidence of extra ribs.

A statistically insignificant increased incidence of extra ribs was observed in rats exposed by inhalation to 1,000 mg/m³ toluene for 24 hours per day on days 7-14 of gestation (Tatrai *et al.*, 1980). Fused sternbrae and extra ribs were observed in rats exposed to 400 ppm (1,500 mg/m³) toluene for 24 hours per day on days 9-14 of gestation (Hudak and Ungvary, 1978). Skeletal retardation was observed in rats exposed to 266 ppm (1,000 mg/m³) toluene for 8 hours per day on days 1-21 of gestation and to 400 ppm (1,500 mg/m³) 24 hours per day on days 1-8. This same group exposed mice to 400 ppm (1,500 mg/m³) or to 133 ppm (500 mg/m³) toluene for 24 hours per day on days 6-13 of gestation. All dams died at the higher dose and a statistically significant decrease in fetal weight was observed at the lower dose.

Skeletal retardations were observed in the offspring of pregnant rabbits exposed by inhalation to concentrations of toluene ranging from 30 to 300 ppm (100 to 1,000 mg/m³), 6 hours per day on days 6-18 of gestation (Klimisch *et al.*, 1992). These results were not dose-dependent and were not reproduced in two additional groups of rabbits exposed to 100 and 500 ppm (400 and 2,000 mg/m³) toluene.

A statistically significant increase in the number of animals showing a 13/13 rib profile (which is considered normal) was observed in mice exposed to 400 ppm (1,500 mg/m³) toluene, 7 hours per day on days 7-16 of gestation (Courtney *et al.*, 1986). An increased number of resorptions was observed in mice exposed to 400 ppm toluene on days 6-15 of gestation (Gleich and Hofman, 1983); the daily exposure duration was not specified.

These preceding animal studies support the association between toluene exposure and effects on somatic development of the fetus. However, the value of these studies is limited by issues such as unknown or unconventional exposure durations, inadequate descriptions of maternal toxicity, use of individual offspring instead of litters for statistical analyses, and purity of toluene used (Donald *et al.*, 1991).

The best available study relating toluene exposure and retardation of somatic development is one in which adult rats of 2 generations were exposed for 6 hours per day to 0, 100, 500 or 2,000 ppm (0, 375, 1,875, or 7,500 mg/m³) toluene during an 80-day pre-mating period and a 15 day mating period (IRDC, 1985). Adult females of both generations were also exposed on days 1-20 of gestation and on days 5-21 of lactation. The mean body weights of fetuses of both generations of dams exposed to 2,000 ppm were significantly decreased compared to controls. No maternal toxicity was reported. Exposure at this level to the male parent only did not result in any adverse effects. The NOAEL for fetotoxic effects in this study was 500 ppm.

In a recent teratogenicity study by inhalation, Ono *et al.* (1995) exposed pregnant Sprague-Dawley rats to 600 or 2000 ppm toluene for 6 h/day from day 7 to day 17 of pregnancy. The control group inhaled "conditioned" clean air. Maternal exposure to 2000 ppm caused significant toxic effects such as body weight suppression in dams and offspring, high fetal mortality, and embryonic growth retardation. However, no external, internal, or skeletal anomalies were observed in the fetuses of any treated group. In addition, there were no differences in the results of pre- and post-weaning behavioral tests of the offspring. No changes which could be related to toluene were apparent in the 600 ppm group. Thus 600 ppm is a NOAEL in this study.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 9.8 ppm (37,000 µg/m³)

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<i>Study</i>	Andersen <i>et al.</i> , 1983
<i>Study population</i>	16 young, healthy males
<i>Exposure method</i>	inhalation
<i>Critical effects</i>	impaired reaction time and symptoms of headache, dizziness, a feeling of intoxication and slight eye and nose irritation
<i>LOAEL</i>	100 ppm
<i>NOAEL</i>	40 ppm
<i>Exposure duration</i>	6 hours
<i>Extrapolated 1 hour concentration</i>	98 ppm ($40^2 \text{ ppm} \cdot 6 \text{ h} = C^2 \cdot 1 \text{ h}$) (see Table 12 for information on “n”)
<i>LOAEL uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	10
<i>Reference Exposure Level</i>	9.8 ppm (37 mg/m ³ ; 37,000 µg/m ³)

Level Protective Against Severe Adverse Effects

In a 2-generation study, adult rats were exposed for 6 hours per day to 0, 100, 500, or 2,000 ppm (0, 375, 1875, or 7,500 mg/m³) toluene during an 80-day pre mating period and a 15 day mating period (International Research and Development Corporation, 1985). Adult females of both generations were also exposed on days 1-20 of gestation and on days 5-21 of lactation. The mean body weights of fetuses of both generations of dams exposed to 2,000 ppm were significantly decreased compared to controls. No maternal toxicity was reported. The NOAEL for fetotoxic effects in this study was 500 ppm. The NOAEL reported in the study, a chronic exposure study, was in the same concentration range as the LOAELs reported in other acute exposure studies addressing reproductive and developmental toxicity, summarized above. However, because the IRDC study was judged to be methodologically the most sound of all the studies considered for this endpoint (Donald *et al.*, 1991), it was chosen as the basis for the severe adverse effect level. An uncertainty factor of 100 was applied to the NOAEL to account for animal to human extrapolation and for intraindividual variability. The 6-hour exposure serves as the basis for the level protective against severe adverse effects. This yields a 6-hour level protective against severe adverse effects of 5 ppm (19 mg/m³).

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) reports an IDLH for toluene of 500 ppm. According to NIOSH, “It has been reported that extreme fatigue, mental confusion, exhilaration, nausea, headache and dizziness resulted from exposures to 600 ppm by the end of 3 hours [von Oettingen *et al.* 1942]. In addition, the following observations have been made: some workers will tolerate concentrations ranging up to 200 ppm for 6 to 8 hours daily with no demonstrable ill effects; 200 to 500 ppm for 6 to 8 hours will cause tiredness and lassitude in most workers; and concentrations over 500 ppm

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for 1 to 3 hours are definitely dangerous and will cause symptoms attributable to depression of the central nervous system and the bone marrow [Wilson 1943]. It has also been reported that exposure to concentrations greater than 4,000 ppm for more than 5 minutes might limit self rescue ability [ANSI 1973]. After 20 minutes, exposures to concentrations at 300, 500, or 700 ppm resulted in significant increases in reaction times; a significant decrease in perceptual speed resulted after a 20-minute exposure to 700 ppm [Gamberale and Hultengren 1972]. The revised IDLH for toluene is 500 ppm based on acute inhalation toxicity data in humans [Gamberale and Hultengren 1972; von Oettingen *et al.* 1942; Wilson 1943].” Based on its documentation, the IDLH of 500 ppm, designed for a 30 minute exposure, does not appear to be low enough to protect the general public, especially sensitive individuals, from life-threatening effects for 1 hour. Therefore, no recommendation for a level protective against life-threatening effects is made at this time.

VII. References

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